Steroid Hormones & the Adrenal Cortex

BCH 120 — Metabolic & Endocrine Biochemistry · Dr. Radi

By the end of this unit, you can…

- Classify the steroid hormone families (glucocorticoids, mineralocorticoids, androgens, estrogens) and explain why cholesterol is their precursor
- Outline cholesterol synthesis from acetyl-CoA (four stages; HMG-CoA reductase as the committed, statin-targeted step)
- Describe adrenal-gland morphology — the cortical zones (glomerulosa/fasciculata/reticularis = salt/sugar/sex) and the medulla
- Trace steroidogenesis: the rate-limiting cholesterol → pregnenolone step (StAR, P450scc) and the enzymatic path to aldosterone, with structures
- Explain aldosterone's action on the kidney, the renin–angiotensin–aldosterone system (renin, ACE, angiotensin II), and clinical disease (Conn's, Addison's) with drug targets (ACE inhibitors, ARBs)

Today's route

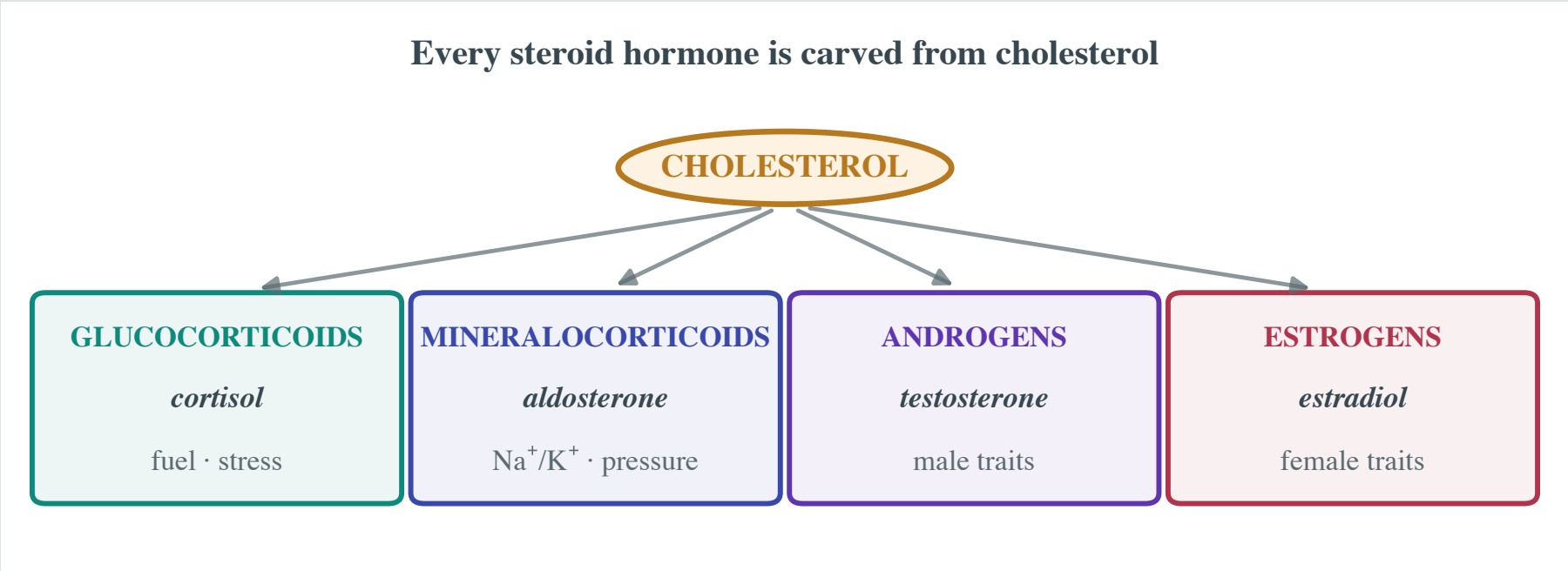
1. Steroid Hormone Families
2. Making Cholesterol from Acetyl-CoA
3. The Adrenal Gland
4. Steroidogenesis – Pregnenolone to Aldosterone
5. Aldosterone, RAAS & Clinical Disease

1 · Steroid Hormone Families

"Every steroid hormone in your body — the stress hormone, the salt hormone, the sex hormones — is carved from one molecule: cholesterol. Small edits to a shared four-ring core give wildly different messages."

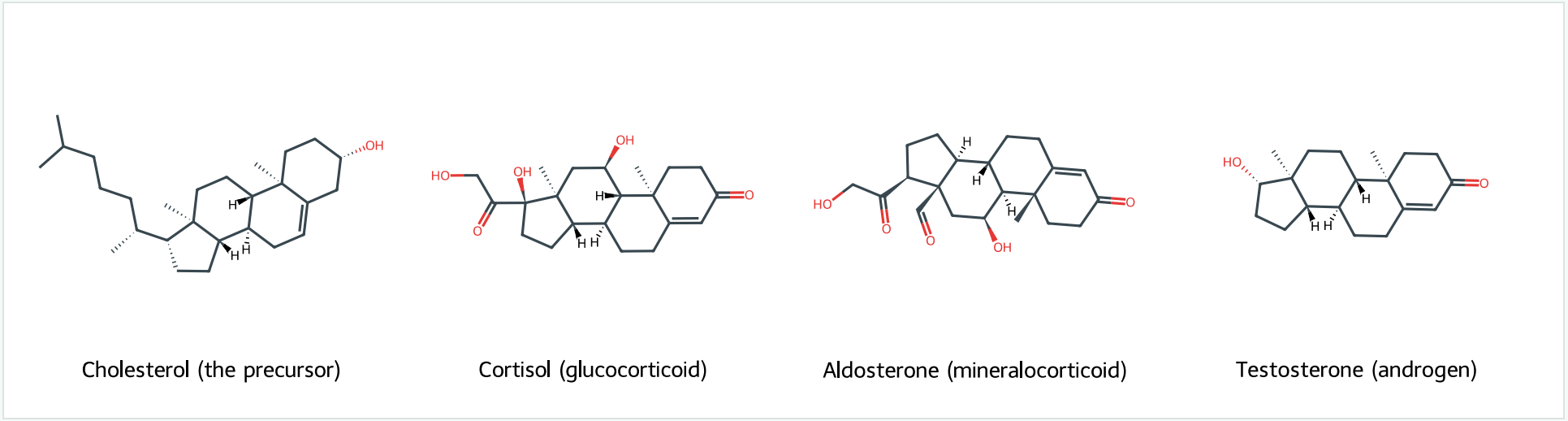
The steroid hormone families

There are just a few **steroid hormone families**, all built on the same skeleton. **Glucocorticoids** (**cortisol**) run **fuel metabolism and the stress response**. **Mineralocorticoids** (**aldosterone**) control **sodium, potassium, and blood pressure**. **Androgens** (**testosterone**) and **estrogens** (**estradiol**) drive **sexual development**. Different jobs, one origin — and because they're all **lipid-soluble**, they all work the slow way: cross the membrane, bind a **nuclear receptor**, change gene expression.



One core, four very different messages

Look at how little separates them. **Cholesterol** — the greasy membrane lipid with its **four fused rings** and a long tail — is the **precursor to every steroid hormone**. Snip the tail and add a few oxygens and you get **cortisol**; a few edits more and it's **aldosterone**; strip more carbons and it's **testosterone**. The **four-ring core is conserved**; the tiny decorations around it are the whole difference between "raise blood sugar" and "build muscle." Structure really is function here.

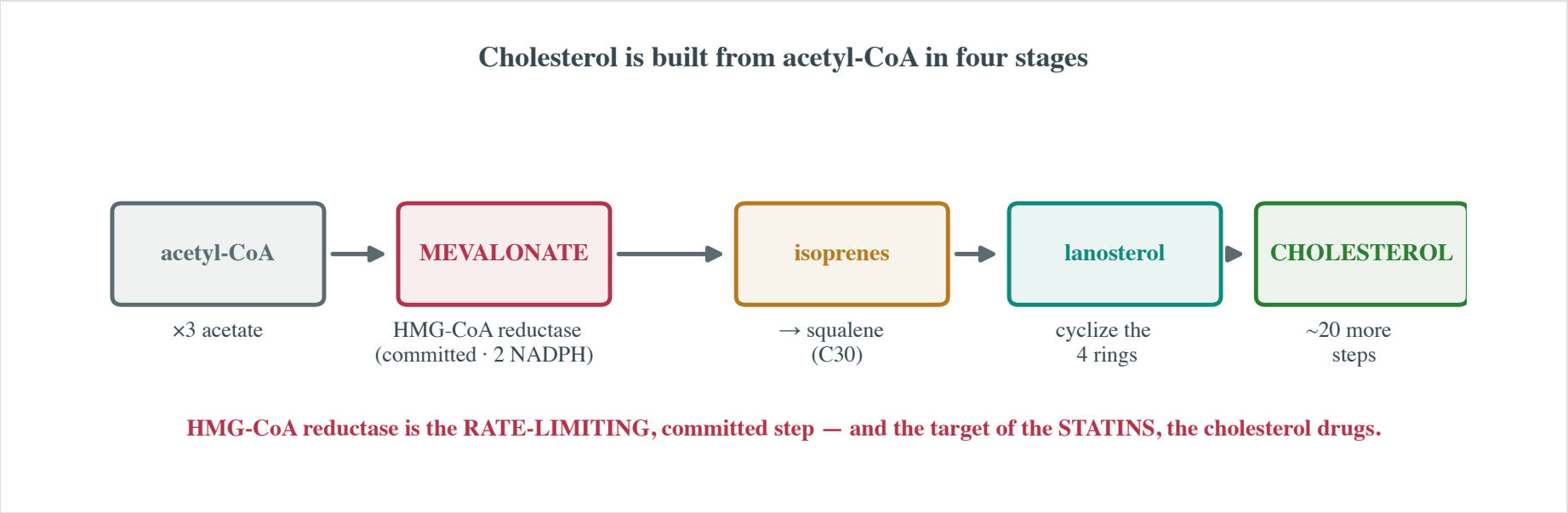


2 · Making Cholesterol from Acetyl-CoA

"Before cholesterol can become a hormone, it has to be built — and the body makes it from the simplest possible start, acetyl-CoA, in four stages. One enzyme in that path is the rate-limiter, the drug target, and the reason statins exist."

Four stages from acetyl-CoA to cholesterol

Cholesterol looks complicated, but the body builds it from **two-carbon acetyl-CoA** in **four stages**. ① Three acetates condense into **mevalonate**. ② Mevalonate is activated into **isoprene** units (using ATP). ③ Six isoprenes polymerize into the 30-carbon chain **squalene**. ④ Squalene folds up and **cyclizes into the four-ring steroid nucleus** (lanosterol), then ~20 more steps finish **cholesterol**. The key control point is the **committed** step, **HMG-CoA reductase** — which uses **2 NADPH** and is exactly where the **statins** act to lower cholesterol.



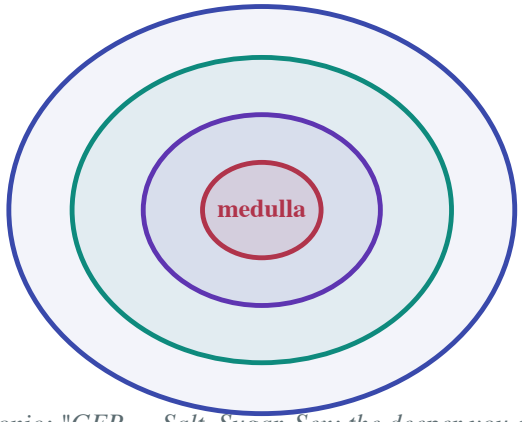
3 · The Adrenal Gland

"The adrenal gland is a two-in-one organ, and its layered anatomy IS its function. Learn the three cortical zones with one mnemonic and you know which steroid comes from where — plus the cautionary tale of anabolic steroid abuse."

Three zones, three steroids

The adrenal gland is **two organs in one**: an outer **cortex** (most of the mass) that makes **steroids**, wrapped around an inner **medulla** that makes **catecholamines** (last unit). The cortex is layered into **three zones**, and one mnemonic nails them: **"GFR — Salt, Sugar, Sex."** **G**lomerulosa → **aldosterone** (**salt**). **F**asciculata → **cortisol** (**sugar**). **R**eticularis → **androgens** (**sex**). The adrenals are **required for life** — lose them and electrolytes and fuel metabolism collapse.

The adrenal cortex: three zones, three steroids

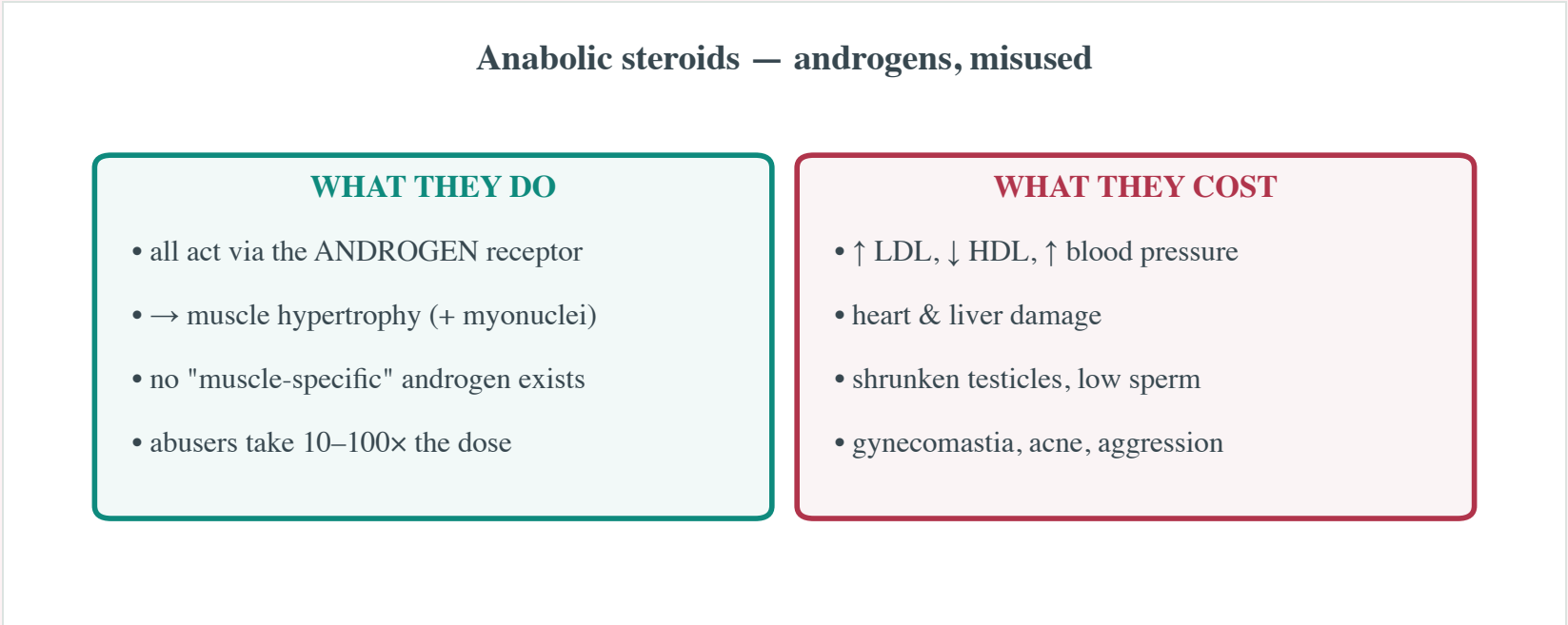


G — zona Glomerulosa	→ aldosterone	**SALT**
F — zona Fasciculata	→ cortisol	**SUGAR**
R — zona Reticularis	→ androgens	**SEX**
Medulla (inner)	→ epinephrine / NE	

Mnemonic: "GFR — Salt, Sugar, Sex; the deeper you go, the sweeter it gets." Cortex = steroids, medulla = adrenaline.

The dark side: anabolic steroids

Because androgens **build muscle**, they get abused — and the biochemistry explains both the gains and the damage. All androgens act through **one androgen receptor** regulating the same genes, so there's **no "muscle-specific" steroid** — just testosterone and its relatives, taken at **10–100× normal doses**. The muscle hypertrophy is real; so is the cost: **raised LDL and blood pressure, heart and liver damage, shrunken testicles, gynecomastia, acne, and aggression**. The receptor can't tell "athlete" from "patient" — it just runs the program.

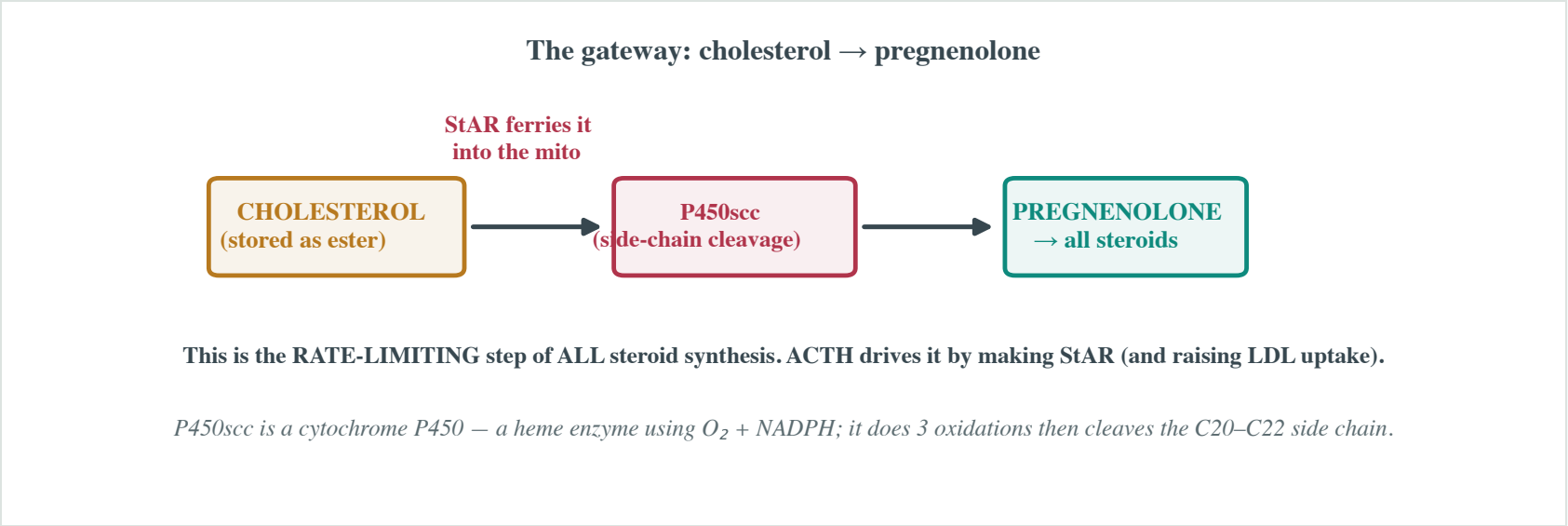


4 · Steroidogenesis — Pregnenolone to Aldosterone

"All steroid synthesis funnels through one gateway molecule — pregnenolone — and that first step is the rate-limiter for the whole system. From there, a march of enzyme edits builds aldosterone, and you should know the names and structures."

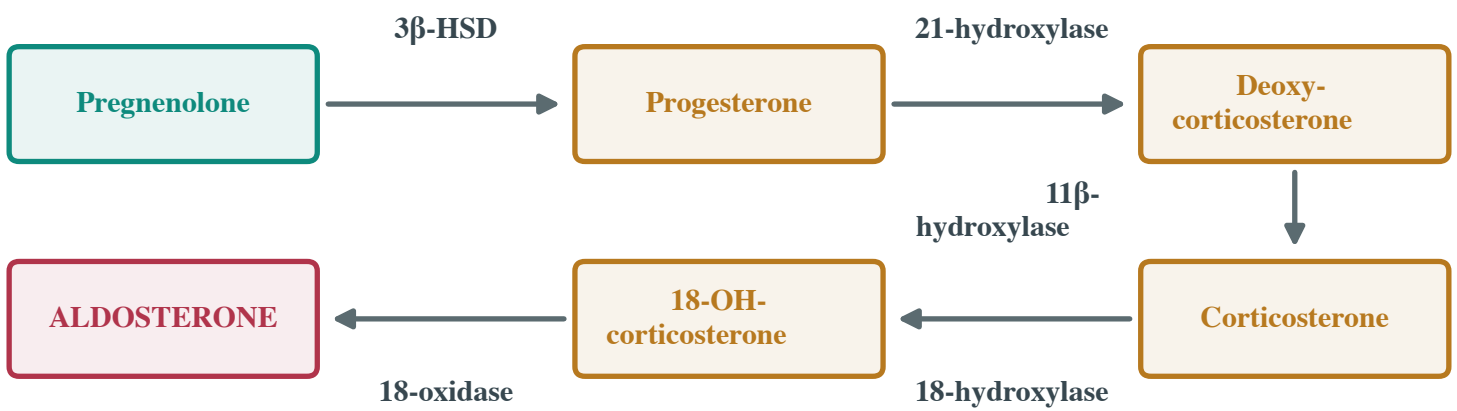
The gateway: cholesterol → pregnenolone

Every steroid begins the same way, and this **first step is the rate-limiter** for the whole system. Cholesterol (stored as an ester) must be **ferried into the mitochondrion** by the short-lived **StAR protein** — and **that transport** is what sets the pace. Inside, the enzyme **P450scc** (side-chain cleavage) performs **three oxidations** and snips off the tail, producing **pregnenolone**, the parent of **all** the adrenal steroids. **ACTH** turns the whole thing up by inducing **StAR** (and raising LDL uptake).



The march to aldosterone

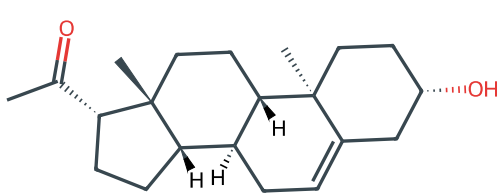
In the **zona glomerulosa**, pregnenolone is walked to **aldosterone** by a chain of enzyme edits — mostly **cytochrome-P450 hydroxylations**. First **3β-HSD** converts pregnenolone to **progesterone**. Then **21-hydroxylase** makes **deoxycorticosterone**, **11β-hydroxylase** makes **corticosterone**, and two final mitochondrial steps (**18-hydroxylase**, then **18-oxidase**) cap it off as **aldosterone**. Know the names in order — and note the clinical hook: a **21-hydroxylase defect** is the most common cause of **congenital adrenal hyperplasia**.



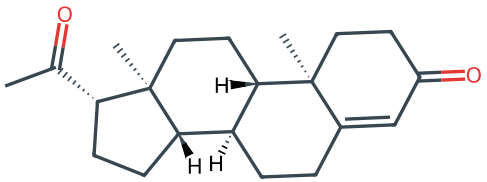
Mostly cytochrome-P450 hydroxylations; the last two (mito) steps finish aldosterone.

Know these structures

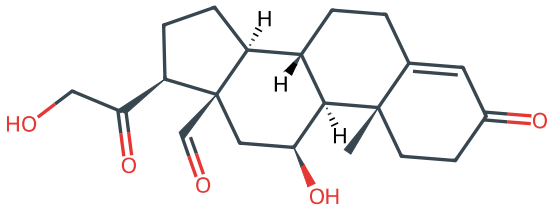
Here are the key players you should be able to recognize. **Pregnenolone** — cholesterol with the tail cut to a short acetyl group and a 3-OH. **Progesterone** — the same, but 3β-HSD has flipped the A-ring to the **3-keto, Δ4** pattern you'll see on almost every active steroid. And **aldosterone** — the finished mineralocorticoid, marked by its distinctive **C18 aldehyde**. Watch the ring core stay constant while the decorations change; that's the whole logic of steroidogenesis.



Pregnenolone



Progesterone (3B-HSD)



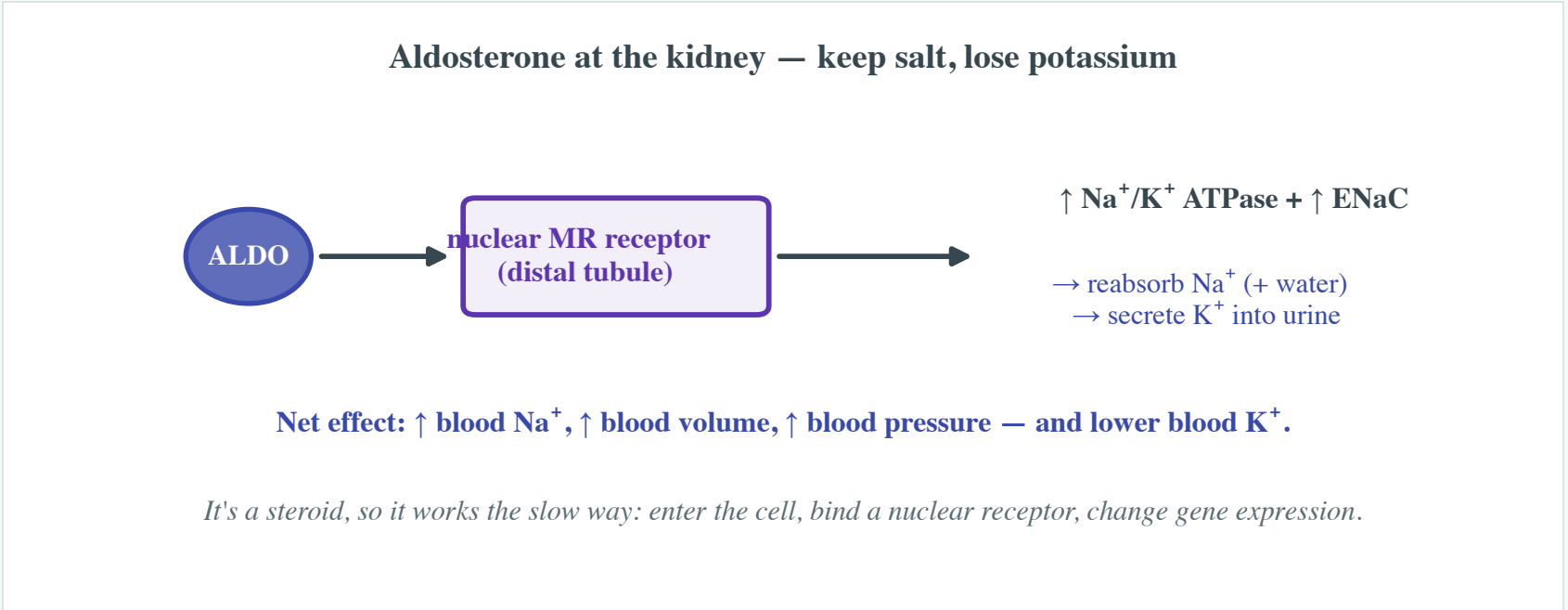
Aldosterone

5 · Aldosterone, RAAS & Clinical Disease

"Aldosterone is your blood-pressure hormone, and it sits at the end of the body's master pressure circuit — the renin-angiotensin-aldosterone system. Understand RAAS and you understand the biggest class of blood-pressure drugs and two classic adrenal diseases."

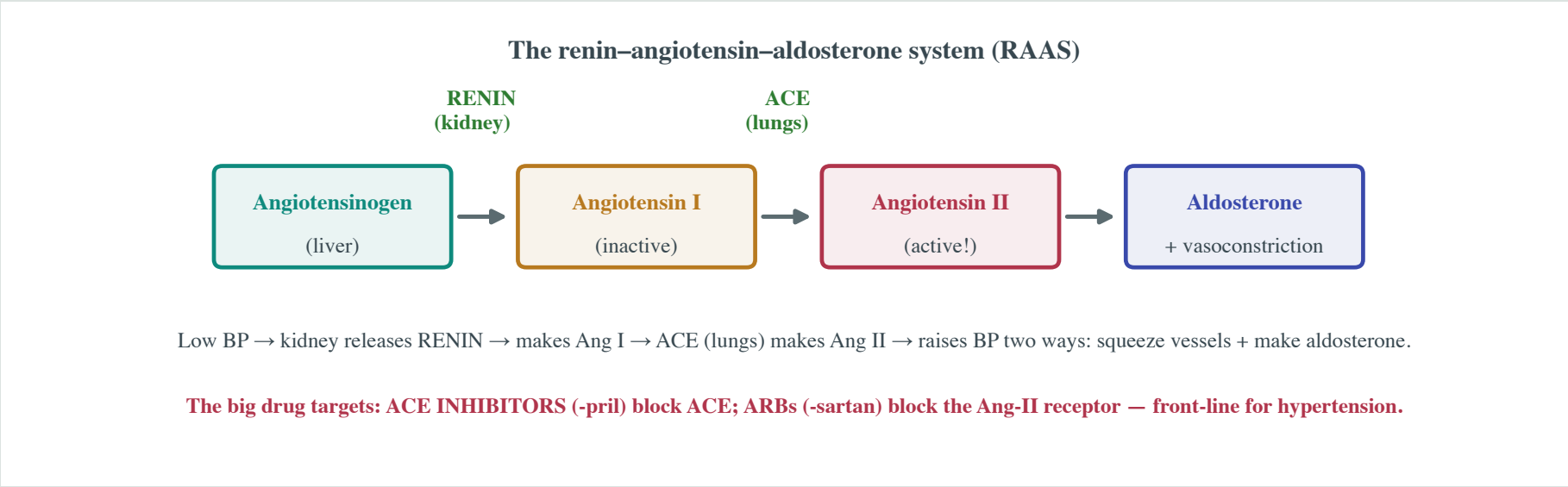
What aldosterone does: keep salt, lose K^+

Aldosterone's whole job is **fluid and electrolyte balance**. It acts on the **distal tubule and collecting duct** of the kidney, and – being a steroid – it works the slow way: bind the **nuclear mineralocorticoid receptor (MR)** and change gene expression. The result is **more Na^+/K^+ ATPase pumps** and **more ENaC sodium channels**, which **reabsorb Na^+ (and water follows)** while **secreting K^+** into the urine. Net effect: **higher blood sodium, volume, and pressure – and lower blood potassium**.



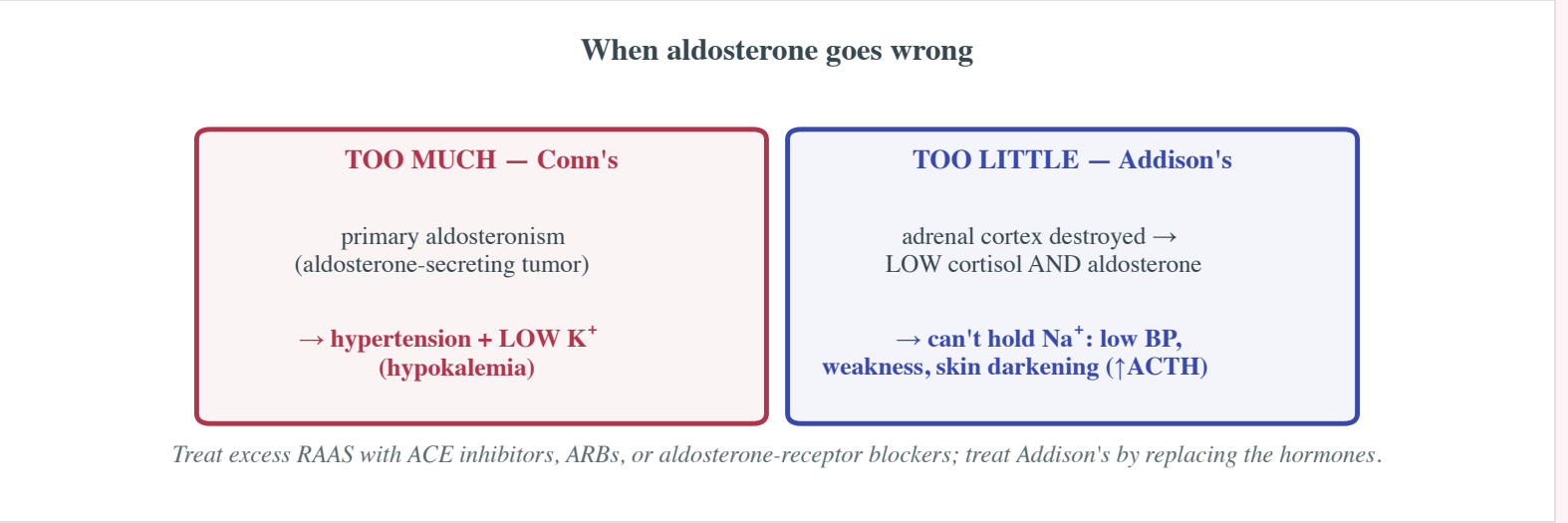
RAAS – the blood-pressure cascade

Aldosterone doesn't act alone; it's the end of the **renin-angiotensin-aldosterone system**. When blood pressure drops, the **kidney releases renin** (sensing low pressure, low Na^+, or sympathetic drive). Renin cleaves liver **angiotensinogen** into **angiotensin I**; then **ACE** (mainly in the **lungs**) converts it to **angiotensin II** – the active hormone. Angiotensin II raises pressure **two ways**: it **constricts blood vessels** (via Gq) **and triggers aldosterone**. This cascade is why the biggest BP drugs are **ACE inhibitors (-pril)** and **ARBs (-sartan)**.



When aldosterone goes wrong

Two diseases sit at the extremes. **Too much** — **Conn's syndrome** (an aldosterone-secreting tumor) — drives **hypertension with low K^+ (hypokalemia)**. **Too little** — **Addison's disease** — is a **destroyed adrenal cortex**, dropping **both cortisol and aldosterone**: the body **can't hold sodium**, so BP falls, with weakness and **skin darkening** (from compensating high ACTH). Treat over-active RAAS with **ACE inhibitors or ARBs** (front-line for **hypertension and heart failure**); treat Addison's by **replacing the hormones**.



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If any box stays empty, the practice site has a drill for it.
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